male and female. The endocrinal conditions under which further differentiation of the genital system occurs, and the effects of hormones on this differentiation, are discussed later.

DEVELOPMENT OF THE GONAD AND FATE OF THE MESONEPHROS

The histologically recognizable primordia of the sex glands appear, in embryos of 4–5 mm. C.R. length, as thickenings (*genital ridges*) of the coelomic epithelium on the medial aspect of the mesonephros immediately after the coelomic lining in this region has transformed itself into an epithelium. When the genital thickenings differentiate in the coelomic epithelium the basement membrane separating the latter from the underlying mesenchyme disappears and cords of cells proliferate from the epithelium into the mesenchyme (Figs. 361 and 362). The gonad now consists essentially of mesodermal cells of coelomic epithelial origin. Soon, however, cells of a special type become apparent interspersed in the substance of the gonadal primordium. These cells are spherical and are distinctly larger than the surrounding mesenchymal cells; they possess large vesicular nuclei and their abundant cytoplasm is difficult to fix properly and is less eosinophilic than that of the mesenchymal cells. These special cells are called *primordial germ cells* (*gonocytes*) and, as will be discussed shortly, they are now generally believed to migrate secondarily to the region of the genital ridges from the wall of the yolk sac (p. 402). The gonads, therefore, are derived from three different components, the primordial germ cells, the coelomic epithelium and the subjacent mesenchyme of a limited part of the mesonephric ridge. Until late in the sixth week of development (embryos of 17–20 mm. C.R. length) the developmental changes in the gonadal ridges are indistinguishable in the two sexes. The cells form a condensation, the *genital blastema*, which extends over about the middle two quarters of the medial aspect of the mesonephros. The mesonephros is now projecting into the coelomic cavity, possessing a thick mesentery which is separated from the root of the gut mesentery by a *medial coelomic bay* and from the parietal coelomic epithelium by a *lateral coelomic bay* (Figs. 344 and 361). Since this mesentery suspends both the mesonephros and the attached genital blastema, it is called the *urogenital mesentery*. The mesentery, the mesonephros and the gonad together make up the *urogenital ridge*.
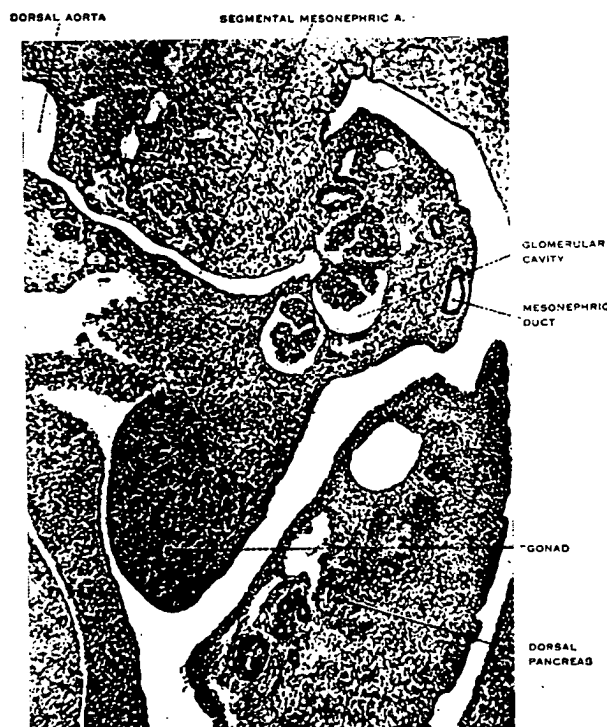

Fig. 362.—A transverse section through the cranial part of the left developing mesonephros and gonad in a 14 mm. human embryo. In the gonad the sex cords appear as darly stained strands. × c. 60.

In the course of subsequent development the urogenital ridge undergoes important modifications (Figs. 361 and 363). As the gonad increases in size, and projects from the medial aspect of the common urogenital ridge, deep grooves appear on its lateral and medial aspects partially separating it from the retrogressing mesonephros laterally and the suprarenal primordium dorsomedially. Deepening of these grooves results in the formation of a gonadal mesentery (*mesovarium* or *mesorchium*) and the urogenital mesentery becomes attenuated. As the gonad is related only to the intermediate portion of the mesonephros, the urogenital ridge

cranial and caudal to the gonad is less prominent and does not show the perigonadal grooves (Fig. 390). The mesonephric part of the original urogenital ridge now shows a ventro-lateral (tubal) portion, containing the mesonephric and parameson-ephric ducts, and a dorso-medial part in which are situated the retrogressing mesonephric tubules (Fig. 363).

The development of the supra-renal gland (p. 518) and metan-phros and the growth of the gonad use the urogenital mesentery, originally lying parallel to the verte-bral column in the sagittal plane, to be displaced laterally especially in its cranial portion (Figs. 390 and 391). In the caudal, *tubal*, part of the urogenital ridge, the medial in-clination of the paramesonephric and mesonephric ducts results in the ridge approaching its fellow of the opposite side and eventually fusing with it thereby forming, in the coronal plane, the *urogenital septum* which lies between the bladder ventrally and the hindgut dorsally (Figs. 364 and 378). As the tubal portion of the urogenital ridge passes the brim of the embryonic pelvis it is joined to the anterior abdominal wall by a mesodermal thickening, the *inguinal fold* or *plica inguinalis* (Figs. 363, 390 and 391), in which the *gubernaculum* of the testis, or ovary, later develops.

Primordial Germ Cells. Problems of major biological impor-tance in the developmental history the gonads are the origin of the primordial germ cells and the rela-tion of these cells to the definitive germ cells. Many investigators of invertebrates and infra-mammalian vertebrates have demonstrated con-clusively that there is an early segre-gation, during development, of those cells which give rise to all the subse-quent sex cells of the organism (Heg-ner, 1914; Bounoure, 1939; and Nieuwkoop, 1949). In reptiles and birds the primordial germ cells are
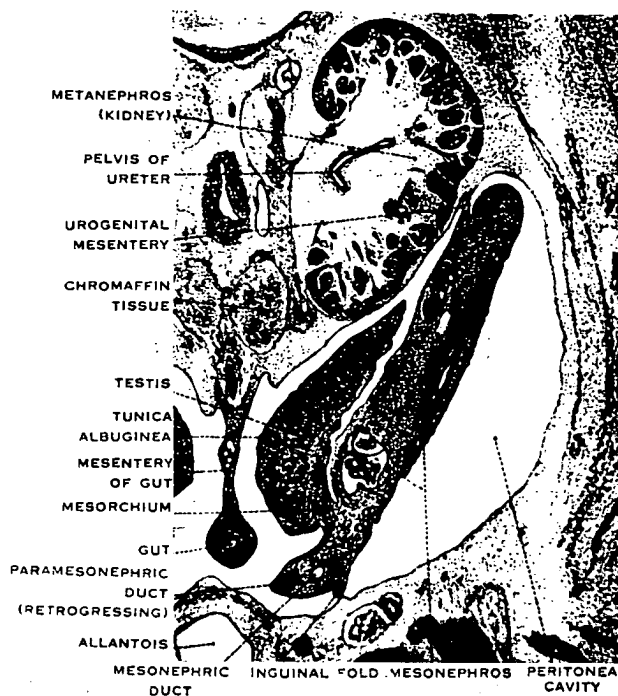

FIG. 363.—A transverse section of the left metanephros, testis and retrogressing mesonephros in a 26 mm. male human embryo.   × c. 45.
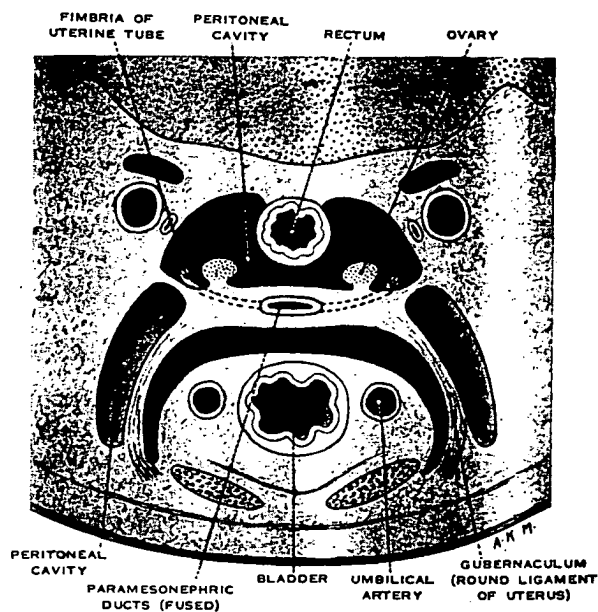

FIG. 364.—A semi-schematic drawing of the pelvic cavity (seen from above) to show the development of the uro-genital septum.
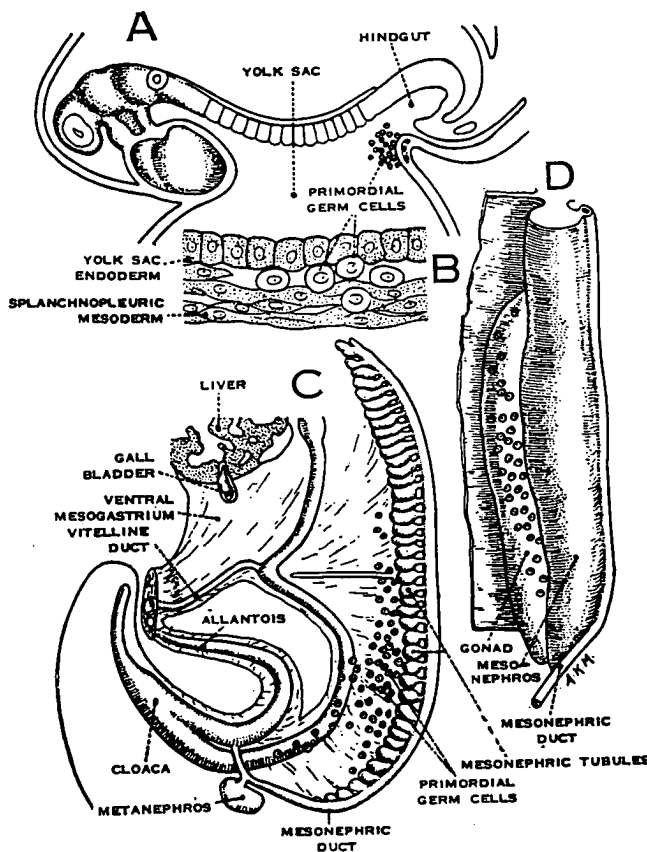
FIG. 365.—Schemes to show the development and migration of the primordial germ cells. A—16-somite human embryo; B—primordial germ cells between the yolk sac endoderm and the splanchnopleuric mesoderm; C— 4·2 mm. human embryo; D—germ cells in the developing gonad. (Based on reconstructions by Witschi.)

first found in the extra-embryonic portion of the yolk sac endoderm. From here they pass, by active amoeboid migration, into the body of the embryo proper. In some birds they pass into the embryo largely by way of the blood stream (Swift, 1914; Simon, 1957) and in late somite stages settle in the region of the germinal epithelium where they proliferate during subsequent development to form the forerunners of all ova or sperms.

An early segregation of the primordial germ cells has also been described in mammals. Several investigators (e.g., Fuss, 1912; Hamlett, 1935; Witschi, 1948; Pinkerton et al., 1961) described primordial germ cells in early human embryos and suggested that they take origin, in the pre-somite stage, either from the endoderm or the overlying mesoderm in a restricted area of the yolk sac wall close to the allantoic diverticulum and later migrate through the mesentery to the region of the germinal epithelium or the gonadal blastema. In Man these cells appear to migrate from the yolk sac to the hindgut wall and thence along its mesentery to the gonadal ridge (Fig. 365) where they become concentrated (Witschi, 1948; Pinkerton et al., 1961). The primordial germ cells thus come secondarily into relation with the other two components, coelomic epithelium and mesenchyme, of the gonad. Other investigators have denied that such primordial germ cells exist, or, if they do exist, that they are concerned with the development of the definitive sex cells (Stieve, 1927; Simkins, 1928; and Swezy and Evans, 1930). The histochemistry of the primordial germ cells (Baxter, 1950; McKay et al., 1953; Chiquoine, 1954; Pinkerton et al., 1961; and see Figures 366 and 367), however, and other investigations (Wolff, 1964) suggest that in mammals, too, there is a precocious segregation of the cells which give origin to the future functional ova or sperms.

It has been shown in the mouse that primordial germ cells are first found in the gut endoderm and later migrate to the genital ridge epithelium (Everett, 1943, 1945). The ova present in post-embryonic life are derived from these cells, which enlarge and then migrate into the ovarian cortex. If genital ridge tissue, before sex cells have developed in it, is transplanted to host kidney, the ridge fails to form sex cells although the associated genito-urinary ducts will develop. Transplants of genital ridge, after sex cells have reached it, form typical testicular or ovarian tissue. A study of mice with gene-induced modifications of the primordial germ cells also supports the interpretation of the significance of these cells which has been accepted here (Mintz, 1957; Mintz and Russell, 1957).

Fig. 366.—Transverse section of a 5 mm. human embryo showing the naphthyl alkaline phosphatase reaction. Primordial germ cells, stained darkly, can be seen in the coelomic epithelium and the connective tissue of the mesentery. A few of the cells have reached the region of the gonadal anlage. × c. 65.

Fig. 367.—Transverse section of an ovary of a 35 mm. human fetus showing the naphthyl alkaline phosphatase reaction in the primordial germ cells. Most of the primordial germ cells are situated in the future cortex of the ovarian blastema. A primitive ovarian medulla is present. (Figs. 366 and 367 reproduced by the courtesy of Prof. A. T. Hertig.) × c. 80.

In the complete absence of primordial germ cells, following experimental ablation, the gonadal ridges usually do not develop. Hence these cells must have some inductive effect on the gonadal mesenchymal blastema. The relationship, however, is a reciprocal one, for while the germinal ridges do not develop in the absence of primordial germ cells, these cells cannot, it would seem, persist unless they come to be included in the appropriately differentiated, or prepared, mesenchyme of the ridges.

HISTOGENESIS OF THE GONADS

Testis. Before the seventh week of embryonic life the gonads of both sexes are identical in appearance so that an examination of their structure does not permit a diagnosis of sex to be made. The testis can first be identified as such in embryos of about 17 mm. C.R. length when the male gonadal blastema becomes subdivided into sex cords by the development of fibrous tissue bundles (Fig. 361). The sex cords are first joined to the germinal epithelium and may, indeed, be derived from it. At about the 25 mm. stage the development of a dense fibrous layer, the *tunica albuginea*, separates the sex cords completely from the germinal epithelium which can, therefore, no longer contribute to them (Fig. 363). Later development results in the inclusion of the male primordial germ cells into the sex cords and in the extension of the latter into the region of the mesorchium where they form a network, the *rete testis*. The cords then become canalized to form the *seminiferous tubules*, the walls of which are formed by the sustentacular (Sertoli) cells surrounding the intercalated primordial germ cells. Some of the shorter cords may not become canalized, and possibly persist as some of the interstitial cells of the testis. Most of the interstitial cells, however, are derived from the mesenchymal cells of the stroma. In fetal life the testicular interstitial cells show marked activity especially in the third, fourth and fifth months (Giroud, 1958). The rete testis becomes canalized relatively late (50–90 mm.) and by further extension into the mesonephric stroma joins some of the mesonephric tubules. Some authors regard the rete as being of mesonephric origin. The five to twelve mesonephric (epigenital) tubules (p. 381) which join the rete testis lose their glomeruli, but persist to form the efferent ductules which bring the rete testis into communication with the mesonephric